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Review article

Infective complication following percutaneous nephrolithotomy[☆]

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ABSTRACT

Percutaneous nephrolithotomy (PCNL) is a minimally invasive procedure for patients with large renal and upper ureteric stones. Although it is less invasive than open surgery, infection is still the most common complication arising from this procedure and some patients develop septicemia and septic shock, resulting in increase in mortality and morbidity. The incidence of septic shock following PCNL is 1%; however, its mortality rate is as high as 66–80%. Endourologists who perform this procedure need to know how to prevent and manage this common complication. Large calculi, staghorn calculi, positive pelvic urine and stone culture, prolonged operative time, and diabetes are factors that increase the incidence of postoperative infection. Recently, several studies suggested the importance of intraoperative microbiologic evaluation of factors such as intraoperative pelvic urine and stone cultures for selection of suitable postoperative antibiotics. The selection of prophylactic antibiotics, postoperative antibiotics, and specific PCNL techniques play an important role in preventing infection following PCNL. We reviewed the general background, the factors, and role of intraoperative microbiologic evaluation in the management of post-PCNL infection.

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1. Introduction

Percutaneous nephrolithotomy (PCNL) is accepted as the procedure of choice for patients with large renal and upper ureteral stones because it is less invasive than open surgery. Advances in medical equipment for PCNL have resulted in a significant reduction in morbidity, mortality, and the cost of treatment. Even with minimal invasiveness, the complications following this procedure are still common. The complications following PCNL are infection, hemorrhage, adjacent organ injury, retained stone, loss of kidney function, and death.

The Clinical Research Office of the Endourological Society (CROES) conducted two multicenter global studies on the complications following PCNL. The data for both studies were collected from experts all over the world working in large endourologic centers in 2011 and 2013, respectively. The first prospective observational study reported on complications of PCNL using the modified Clavien classification system,¹ whereas the second study demonstrated the occurrence of urinary tract infection (UTI) and postoperative fever following this procedure.² The first study included 724 patients, of whom 20.5% experienced some

complications. Complications based on Clavien scores were categorized into either minor complications (Grades I and II) or major complications (Grades III and IV). Eighty percent of all complications were minor, and five risk factors were identified, including American Society of Anesthesiologists status classification III or IV, anticoagulant usage, positive urine microbiologic culture, and concurrent cardiovascular disease (CVD). Major complications including hydrothorax, pneumothorax, pleural effusion, urinary fistula, ureteric obstruction, and urosepsis were less common. Renal insufficiency, diabetes, morbid obesity, and CVD are the common co-morbidities, which increase the possibility of postoperative PCNL complications. Among all complications, fever was the most common complication followed by bleeding; however, most of them were minor and successfully controlled using medications. Specific risk factors that are associated with postoperative UTI are positive intraoperative urine/stone culture, infected stone, neurogenic bladder, higher operative time, and postoperative nephrostomy tube placement.¹

The second CROES PCNL study group reviewed the incidence of UTIs, postoperative fever, and risk factors for post-PCNL fever from 96 centers.² The criterion for postoperative fever was a body temperature higher than 38.5°C. This study investigated a total of 5803 patients, of whom 865 (16.2%) had a positive urine culture. The most common organism isolated was *Escherichia coli* (Gram

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[☆] There are 3 CME questions based on this article.

negative), which was found in 350 patients (6.5%). Post-PCNL fever was noted in approximately 10% (550) of the cases, although the patients received antibiotic prophylaxis. The percentage of post-PCNL fever in patients with negative preoperative urine culture and positive preoperative urine culture was 8.8% and 18.2%, respectively. Postoperative PCNL fever was significantly increased with the increasing mean durations of hospitalization ($3.4 \text{ days} \pm 1.7 \text{ days}$ vs. $5.4 \text{ days} \pm 2.3 \text{ days}$; $p < 0.001$). Postoperative fever is frequently observed in cases with nephrostomy tube placement and in women because the nephrostomy tube, which is used in complicated cases, acts as a foreign body and females have greater risk of UTI.² Both studies demonstrated the importance of preventing infection-related complications following PCNL, and endourologists need to know how to manage these complications.

Of the common complications following PCNL, major complications are noted in 1.1–7% of the patients and minor complications in 11–25% of the patients.³ Perioperative complications following this procedure are observed in up to one third of patients. Fever is the most common complication found in about 21–39.8% of the cases. The temperature cutoff point for fever is 38°C or 38.5°C . The study reported that 39.8% of patients developed a fever within 24 hours of PCNL; however, this rate fell to 13.0% when the patients were assessed beyond 24 hours after PCNL.²

PCNL is categorized as a clean-contaminated or contaminated surgery. Postoperative bacteriuria usually occurs in stone patients with preoperative sterile urine especially in those without prophylactic antibiotic administration. Postoperative sepsis is one of the most serious complications following PCNL and can be caused by bacterial infection from stone or renal pelvic urine, which enters the bloodstream during stone manipulation through pyelovenous, pyelolymphatic, and pyelotubular backflows, and forniceal rupture.⁴ The two components of bacteremia during PCNL are stone colonization by bacteria and the release of endotoxin as lipopolysaccharide during stone fragmentation and continuous fluid irrigation by small vein and lymphatic channels.^{5–8}

Serious conditions such as urosepsis and septic shock were found in 0.3–9.3% of patients who had a fever complication.⁹ In the International Sepsis Definition Conference 2001, severe sepsis was defined as the presence of a source of infection with systemic inflammatory response syndrome (SIRS). SIRS is considered when patients have more than one of the following findings: body temperature higher than 38°C or less than 36°C , heart rate higher than 90 beats/min, respiratory rate higher than 20 breaths/min or PaCO_2 less than 32 mmHg, and white blood cell count higher than 12,000 cells/mm or lesser than 4000 cells/mm.¹⁰ Most cases of fever following PCNL are minor and easily managed without intervention. However, the concern regarding post-PCNL fever is bacteremia and urinary extravasation, which may develop into septicemia and septic shock that increase morbidity and mortality.^{11,12}

The incidences of postoperative fever and bacteremia are 20–35% and 0–59%, respectively. This means that postoperative fever is not necessarily indicative of postoperative UTI. Postoperative fever can be caused by other conditions such as obstruction of nephrostomy tube, myocardial infarction, ulnar nerve palsy, air embolism, and arteriovenous fistula requiring embolism.¹²

Postoperative UTI usually occurs in patients with urethral catheter, nephrostomy tube placement, obstructed collecting system, calculus-bearing bacteria, and blood transfusion. Sepsis usually follows bacteremia or endotoxemia and stimulates inflammatory cascade resulting in septic shock. The incidence of septic shock after PCNL is 1%, but the mortality rate is as high as 66–80%.¹³

Stone patients with neuromuscular disorder have the highest risk of postoperative PCNL complications, especially infective complications. In their study on 35 PCNL patients with

neuromuscular disorder, Eswara et al¹⁴ compared the infection rate between patients receiving same-day PCNL and delayed PCNL (pre-nephrostomy tube placement for 24 hours). Patients with neuromuscular disorder in their study included 16 with multiple sclerosis, 10 with spinal bifida, four with quadriplegia, three with paraplegia/Guillain–Barré syndrome, and two with cerebral palsy. All patients had negative urine culture and received antibiotics for 4–7 days before surgery. The rates of sepsis/bacteremia in the same-day PCNL and delayed PCNL patients were 26% and 0%, respectively (odds ratio 8.4; $p = 0.05$). They recommended delayed PCNL in patients with neuromuscular disorder to prevent postoperative bacteremia and sepsis.¹⁴

2. Risk factors affecting infection complication following PCNL

Factors affecting the risk of postoperative sepsis are divided into preoperative, intraoperative, and postoperative factors.

- *Preoperative factors* include positive preoperative urine culture, positive intraoperative urine culture, stone size, infected stone, neurogenic bladder dysfunction, and abnormality of renal anatomy.
- *Intraoperative factors* include renal pelvic pressure and operative time.
- *Postoperative factors* include nephrostomy tube placement, urethral catheter placement, and antibiotic administration.

Reports on various factors that increase the risk of postoperative fever are presented in Table 1.^{2,5,11,13,15–20}

3. Role of preoperative and intraoperative microbiologic assessment

Preoperative urine culture may be sterile due to the obstruction of urinary system. Approximately 10.1% of perioperative urine cultures (intraoperative pelvic urine) were positive in patients with negative preoperative urine culture in a previous study.¹³ A perioperative urine sample is the urine collected when the first percutaneous needle accesses the collecting system. In that study, a total of 21 of 82 PCNL patients with postoperative fever were negative for both preoperative and perioperative cultures.¹³

Post-PCNL fever in preoperative sterile urine is caused by perioperative antibiotics that suppress the growth and inhibits colony formation of bacteria. Bactericidal antibiotics increase plasma endotoxins by lysing bacterial cells, consequently releasing pyrexia-related endotoxin and inflammatory mediators (not microbial).¹³ This release of inflammatory mediators can cause low-to-moderate fever. Clinical presentation is common in patients with negative preoperative urine culture who received preoperative antibiotics.¹³ Even in patients with preoperative sterile urine, urosepsis following PCNL may occur due to the release of bacterial endotoxins and viable bacteria during stone fragmentation.²¹ Organisms isolated from crushed stones are different from those from urine. Urinary calculi can serve as the nidus for bacteria, and stone culture should be the best indicator for identifying the actual microorganisms.⁵

Several studies have shown the different importance of preoperative and intraoperative microbiologic assessments in PCNL. Cadeddu et al¹² demonstrated that bacteriologic evaluation was unnecessary in hemodynamically stable and negative preoperative urine culture patients who were treated prophylactically with immediate preoperative antibiotics and maintained on postoperative antibiotics. In their study, eight patients (12%) had fever between 38.0°C and 38.5°C , whereas 11 patients (16.7%) had fever greater

Table 1
Factors that increase the risk of postoperative fever.

Study	Risk factors
Gutierrez et al ²	Positive urine culture (OR = 2.12) Staghorn calculi (OR = 1.59) Preoperative nephrostomy (OR = 1.61) Lower patients age (OR for each year of 0.99) Diabetes (OR = 1.38)
Margel et al ⁵	Stone culture
Gonen et al ¹¹	Stone culture Pelvic urine culture Large stone size Operative time
Dogan et al ¹³	Pelvic urine culture Stone culture
Sharifi Aghdas et al ¹⁵	Female sex Positive urine culture Nephrostomy tube placement
Eswara et al ¹⁶	Stone culture
Lojanapiwat and Kitaratrakarn ¹⁷	Preoperative urine culture Pelvic urine culture Stone culture
Healy and Ogan ¹⁸	Staghorn calculi
Wang et al ¹⁹	Preoperative urine white blood count Operative time (OR time > 90 min, $p = 0.017$)
Draga et al ²⁰	Previous PCNL (OR = 3.1) Paraplegia (OR = 10.7)

OR = odds ratio; PCNL = percutaneous nephrolithotomy.

than 38.5°C. All patients had negative postoperative blood and urine cultures. Another study demonstrated that there was no association between postoperative fever and stone composition or postoperative white blood cell.³ Stone and pelvic urine culture are more useful for identifying stone-colonizing pathogen compared with preoperative urine culture. Fever in post-PCNL patients who are hemodynamically stable showed negative bacteriologic evaluations in both blood and urine cultures.

Mariappan et al⁹ confirmed that bacteria in the stone plays a role in systemic infection. They analyzed 54 cases, and reported positivity rates of mid-stream urine, pelvic urine, and stone culture were 11.1%, 20.4%, and 35.2%, respectively. The percentages of colonization of pelvic urine/stone and positive preoperative urine cultures were 42.6% and 5.6%, respectively. The positive predictive value and negative predictive value of preoperative urine cultures were 5% and 56%, respectively. Patients with positive stone and pelvic urine cultures had four times greater risk of urosepsis. Stone culture is recommended as the best method to predict urosepsis (positive predictive value 0.7).

Eswara et al¹⁶ studied the correlation between urine and stone cultures with postoperative sepsis in 328 patients who received PCNL and ureterorenoscopy. In their study, 11 patients (3%) developed postoperative sepsis, and eight of these patients had positive stone cultures despite all having negative preoperative urine cultures. Postoperative sepsis was found more in patients with positive stone cultures compared to patients with negative stone cultures (8% and 1%, respectively). The same pathogen in stone and urine cultures was found in 64% of postoperative sepsis patients. Stone cultures are more important than a preoperative urine culture in patients receiving preoperative antibiotics because the significant difference in pathogen numbers between stone cultures and urine cultures had been demonstrated.

Lojanapiwat and Kitaratrakarn¹⁷ reported that 56 of 200 patients developed SIRS following PCNL and 11 patients in this group had fever despite all having preoperative negative cultures. Patients with SIRS compared with non-SIRS patients had more positive urine cultures (66.1% and 10.4%, respectively), positive pelvic cultures (46.4% and 3.5%, respectively), and stone cultures (48.2% and 3.5%, respectively).

In a prospective study, Gonen et al¹¹ reported on the preoperative and intraoperative factors affecting post-PCNL fever. The results showed the importance of intraoperative microbiologic evaluation in the selection of postoperative antibiotics. Fever (temperature > 38°C) was found in 16.8% of the patients, and only 1.6% developed fever in association with SIRS. The factors that could be used to predict postoperative fever were stone cultures, pelvic urine cultures, stone size, and operative time. The hospital stay, complication, and number of struvite stones were not different between the febrile and afebrile groups.

Doğan et al²² reported 82 post-PCNL fever cases in their study of 338 patients. The positive urine and blood cultures were noted in 28 (35%) and 9 (11%) patients, respectively. Postoperative fever was significantly different between patients with positive pelvic urine culture/stone cultures and patients with negative cultures ($p < 0.05$).

The role of preoperative and intraoperative cultures in mediating fever/SIRS post-PCNL is shown in Table 2.

Most studies demonstrated the important role of intraoperative pelvic urine and stone culture. The result of these cultures is very helpful in choosing appropriate postoperative antibiotics. The preoperative urine culture is less clinically important, which may be sterile due to the effect of preoperative antibiotics and obstruction of urinary tract.

4. Continuing PCNL in situations with incidental purulent fluids in kidneys

Incidental aspiration of purulent fluids at the time of renal access is occasionally possible even in situations where there is no fever, bacteremia, or recent UTI. In such cases, endourologic intervention should be withheld and physicians should be careful about postoperative sepsis. The general practice in such situations is nephrostomy tube placement until sterile urine is obtained, followed by delayed PCNL. Single nephrostomy tube drainage in one calix may be unable to drain all calices. Rao et al²³ recommended draining and no injection of contrast media, which might lead to sepsis in this situation. The purulent fluid found during renal access is not always infected. In this situation, positive fluid cultures are found in fewer than half of patients with indications of sterile pus. The previous antibiotic usage, a sterile inflammatory tissue in response to calculus and macroscopic crystalline or amorphous calculi may take a role in this condition. Clinical presentation of fever and slight flank discomfort might be insignificant.

Hosseini et al²⁴ reported the efficacy and safety of PCNLs in 45 patients with staghorn renal stones and incidental purulent fluids in the pelvicaliceal system. A total of 29 patients received immediate PCNL, whereas the remaining 16 patients received delayed PCNL (3–5 days later) after nephrostomy tube placement and treatment with antibiotics. In patients who received immediate and delayed PCNL, 10.3% and 12.5% patients, respectively, experienced low-grade fever for 12–24 hours. The percentages of positive fluid culture and positive stone cultures are not different in both groups. *E. coli* was the most common organism in both groups followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The authors concluded that PCNL can be safely performed in this condition with full antibiotic administration.

Etemadian et al³ compared the benefits of immediate PCNL with delayed PCNL in patients with aspirated cloudy urine. Delayed PCNL was performed 10 days after the nephrostomy tube placement. Infected urine was noted in 25% of immediate PCNL and 40% of delayed PCNL cases. No difference in postoperative fever was found after immediate (25%) and delayed PCNL (26.7%). Both groups had the same risk factors (bacteriuria and positive urine culture). The success rate and length of hospital stay were not

Table 2

Role of preoperative and intraoperative cultures in mediating fever/SIRS after percutaneous nephrolithotomy.

Series (N)	Positive preoperative urine culture N (%)	p	Positive pelvic urine culture N (%)	p	Positive stone culture N (%)	p
Margel et al ⁵						
SIRS (17)	2 (11%)	NS	ND	—	13 (76%)	<0.05
Non-SIRS (58)	17 (20%)		ND		23 (40%)	
Gonen et al ¹¹						
Fever (10)	4 (40%)	NS	3 (30%)	<0.05	5 (50%)	<0.05
Nonfever (51)	9 (17.6%)		2 (4%)		9 (17.6%)	
Dogan et al ¹³						
Fever (84)	ND	—	14 (17.1%)	<0.05	47 (57.3%)	<0.05
Nonfever (256)	ND		20 (7.8%)		68 (26.6%)	
Lojanapiwat and Kitirattakarn ¹⁷						
SIRS (56)	37 (66.1%)	<0.001	26 (46.4%)	<0.001	27 (48.2%)	<0.001
Non-SIRS (144)	15 (10.4%)		5 (3.5%)		5 (3.5%)	

ND = not done; NS = no significant difference; SIRS = systemic inflammatory response syndrome.

different between the two groups. They suggested that even if thick pus is aspirated during the initial puncture of PCNL, PCNL can be safely continued using a low-pressure Amplatz sheath and empirical antibiotics.

Aron et al²⁵ reported 19 cases of purulent fluids in kidneys at initial puncture without any signs and symptoms suggestive of infection. Twelve patients had immediate PCNL, of which seven patients had no complication, three cases had transient fever, and two cases had sepsis. The final results of fluid culture were negative in eight patients, *E. coli* infection was found in two cases, and *Proteus* or *Serratia* infection in one case each. There was no postoperative infection in three of the seven cases in the deferred group (3–7 days after nephrostomy tube placement), whereas two cases had transient fever and two had sepsis. Five of seven had sterile fluid.

The risk factors of sepsis in these cases were a recent history of UTI, borderline elevation of total leukocyte count, thick foul pus on initial access, delayed creation of second tracts, and operative time more than 90 minutes. Patients with these factors should have initial nephrostomy tube drainage, and multiple tracts might be needed to drain all blocked calices.³

Several studies have demonstrated the safety of PCNL in cases where incidental purulent fluid was found in kidneys on first access. For these patients, nephrostomy tube placement is indicated, followed by delayed PCNL, especially for those with a recent history of UTI, borderline elevation of total leukocyte count, and thick foul pus on initial access.

5. Prophylactic antibiotic administration in PCNL

The protocols for antibiotic prophylaxis in PCNL are still controversial. In a previous study by Charton et al,²⁶ 107 patients had sterile urine preoperatively and did not receive prophylactic antibiotics, so that the mechanisms of UTI after PCNL could be studied. The rate of postoperative UTI was 35%, of which 10% of the cases presented with fever ($\geq 38.5^\circ\text{C}$).

Inappropriate use of antibiotics leads to antimicrobial resistance, which results in increased morbidity, cost of treatment, and duration of hospital stay. The incidence of postoperative UTI following PCNL with and without prophylactic antibiotics are reported to be 2% and 12%, respectively. The incidence of postoperative fever may be as high as 25.8% in patients without prophylactic antibiotic administration. Sometimes prophylactic antibiotics fail to fully prevent post-PCNL UTI. This failure can be explained by the bacterial resistance to antibiotics and inappropriate use of antibiotics.²

Prophylactic antibiotics are recommended in PCNL procedure because PCNL is a clean-contaminated (uncomplicated stone without obstruction, without stent and without history of UTI) or

contaminated (complex stone with obstruction, nephrostomy tube or double J-stent placement) surgical procedure. Despite the negative preoperative urine cultures, perioperative antibiotic is routinely administered and routine bacteriologic evaluation should be performed when postoperative fever occurs.¹³ The role of prophylactic antibiotics is to only decrease the risk of postoperative infection complications, and they do not completely eliminate the risk of infection.² Periprocedural intravenous antibiotics are administered to reduce local wound and systemic infections. Mariappan et al²⁷ conducted a prospective controlled trial to evaluate whether administration of ciprofloxacin 1 week before PCNL in patients with stones measuring 20 mm or more or dilated pelvicalyceal system significantly reduced the risk of urosepsis. They compared 46 patients without preoperative oral antibiotics and 52 patients who received preoperative oral ciprofloxacin. The treatment arm had three times less risk of upper tract infection [relative risk (RR) 3.4, confidence interval (CI) 1.0–11.8, $p = 0.04$] and SIRS (RR 2.9, CI 1.3–6.3, $p = 0.04$).

In a study by Tuzel et al,²¹ patients with a single dose of prophylactic antibiotic were compared with those with who received a single dose of antibiotic followed by oral administration of third-generation cephalosporin. There was no significant difference in fever episode, positive renal pelvic urine culture, positive stone culture, urine sent for culture on the nephrostomy catheter, and septicemia. None of the patients experienced septicemia in their study. Some reports do not recommend prophylactic antibiotics to prevent post-PCNL fever but do recommend a short course of antibiotics for staghorn stones.¹⁵ Systematic reviews indicate that prophylactic antibiotics are not of advantage when preoperative urine culture is negative. Urine culture is not sensitive for the detection of urinary tract colonization.

The European Urologic Association (EAU) guideline recommends prophylactic antibiotic for percutaneous stone surgery due to the high risk of infection following this procedure (Level 1b, Grade A). Patients with infected stones, a recent history of UTI, and a positive urine culture should receive prophylactic antibiotics prior to undergoing PCNL, which should be continued for at least 4 days postoperatively. The guideline also recommends an appropriate prophylactic antibiotic for sterile urine preoperatively as a means of decreasing the incidence of postoperative sepsis.²⁸

The common organisms isolated following percutaneous stone extraction are Enterobacteriaceae, Enterococci, and Staphylococci. The EAU guideline recommends administration of one of the following in all cases: trimethoprim/sulfamethoxazole, cephalosporin (second or third generation), aminopenicillin/beta-lactamase inhibitors, or fluoroquinolones.²⁸ In some studies, the favored antibiotic prophylaxis is either a single dose of third-generation cephalosporin⁴ or oral ciprofloxacin²⁷ or intravenous ciprofloxacin followed by administration of antibiotics 5–6 days

after the surgery.¹⁶ Different types of organisms are isolated from different specimens such as urine, pelvic urine, and stones. The optimal antibiotic is a broad-spectrum antibiotic for Gram-negative and Gram-positive bacteria. The choice of antibiotics depends on the sensitivity of the antibiogram in the hospital. The drug of choice may be amikacin, ampicillin, vancomycin, or carbapenem in the hospital as most bacteria are resistant to ceftriaxone.¹⁷ The duration of antibiotic administration should be as short as possible to reduce the possibility of bacterial antibiotic resistance, cost of treatment, and duration of hospital stay. A single-dose prophylactic antibiotic is equal to a short-term prophylactic antibiotic.⁴

Prophylactic antibiotics are recommended for patients undergoing percutaneous stone surgery. The duration of antibiotic depends on whether the stone is uncomplicated or complex. The optimal drugs are broad-spectrum antibiotics and depend on sensitivity of antibiogram in the hospital.

6. Strategies for prevention of infective complications

Prophylactic antibiotics and surgical techniques are important in the prevention of postoperative infection following PCNL. Techniques for reducing the risk of postoperative fever include the use of Amplatz sheath for lowering the intrarenal pressure and the use of continuous flow instruments.²⁹ Novel agents for the prevention and treatment of postoperative fever and sepsis are anti-endotoxin antibodies and cholesterol-lowering drugs (e.g., statins).⁹

Prevention of infective complication is very important to decrease the morbidity and mortality following PCNL. Good surgical technique with low intrarenal pressure and proper antibiotic administration is necessary to prevent this common complication.

7. Conclusion

Urosepsis is one of the most serious complications following PCNL. Even in preoperative sterile urine, urosepsis following PCNL may occur due to the release of bacterial endotoxins and viable bacteria during stone fragmentation. Stone culture is the best predictor of urosepsis. A significant difference in the number of different pathogens isolated between stone culture and urine culture is demonstrated, which is very important in clinical practice for selection of suitable postoperative antibiotics. Prophylactic antibiotics is recommended in PCNL procedure owing to its clean contaminated/contaminated surgical procedure.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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